REMARKS/ARGUMENTS

Status of the Claims

Claims 1, 6, 7, 10, 11, 44, 49-51, 108 and 109 were under examination. Claims 44 and 49-51 are withdrawn as drawn to a non-elected invention. New claims 110-114 are added herein. Claims 1, 6, 7, 10, 11 and 108-114 are presently under examination.

Claim Amendments

For convenience, citations to support in the Specification refer to the published application (Publ. No. 20040191248).

New claim 110 is added to recite the composition of claim 1 wherein the naked anti-CEA antibody does not bind to meconium antigen. The amendment is supported in the Specification at least at Paragraphs [0011], [0015], [0048]-[0049], [0097], [0100] and [0126].

New claim 111 is added to recite a composition comprising a naked humanized MN-14 antibody comprising the 6 CDR sequences of MN-14 and human framework and IgG1 human constant regions, wherein administration of the naked hMN-14 sensitizes CEA-expressing cancers to apoptosis agents, and an apoptosis agent wherein the combination of antibody and apoptosis agent shows synergistic effects on human medullary thyroid carcinoma or human colorectal cancer. The amendment is supported at least in original claims 6 and 21, Figures 1, 6, 7, 8, 10-19, 22 and 23 and in the Specification at least at Paragraphs [0003], [0011], [0019], [0048], [0050]-[0052], [0058], [0060], [0069], [0080], [0102], [0104], [0107]-[0114], [0247], [0249], [0250], [0286]-[0288] and [0294] and Examples 2, 6, 7-9 and 14-17.

New claim 112 is added to recite the composition of claim 111 wherein the apoptosis agent is vincristine, doxorubicin, dacarbazine (DTIC), cyclophosphamide, CPT-11, oxaliplatin, 5-fluorouracil/leucovorin, gemcitabine or a combination thereof. The amendment is supported at least by original claim 11 and in the Specification at Paragraphs [0019], [0104], [0107], [0111], [0114] and [0137].

New claim 113 is added to recite a composition comprising a naked humanized MN-14 antibody comprising the 6 CDR sequences of MN-14 and human framework and IgG1 human constant regions, wherein administration of the naked hMN-14 sensitizes CEA-expressing cancers to DTIC or CPT-11, and an apoptosis agent selected from DTIC and CPT-11, wherein the combination of antibody and apoptosis agent shows synergistic effects on human medullary thyroid carcinoma or human colorectal cancer. The amendment is supported at least in original claims 6 and 21, Figures 1, 6, 7, 8, 10-19, 22 and 23 and in the Specification at least at Paragraphs [0003], [0011], [0019], [0048], [0050]-[0052], [0058], [0060], [0069], [0080], [0102], [0104], [0107]-[0114], [0247], [0249], [0250], [0286]-[0288] and [0294] and Examples 2, 6, 7-9 and 14-17.

New claim 114 is added to recite a composition comprising at least one naked humanized, chimeric or human anti-CEA antibody that binds to the same epitope of CEA as a murine MN-14 antibody comprising the 6 CDR sequences of MN-14 and at least one apoptosis agent, wherein administration of the naked anti-CEA antibody to a cancer expressing CEA sensitizes the cancer to the apoptosis agent and the combination of naked anti-CEA antibody and either DTIC or CPT-11 shows synergistic effects on human medullary thyroid carcinoma or human colorectal cancer. The amendment is supported in original claims 6 and 21, Figures 1, 6, 7, 8, 10-19, 22 and 23 and in the Specification at least in the Abstract and Paragraphs [0003], [0010], [0011], [0019], [0048], [0050]-[0052], [0058]-[0062], [0069], [0078]-[0084], [0094], [0096], [0098], [0102], [0104], [0105], [0107]-[0114], [0247], [0249], [0250], [0286]-[0288] and [0294] and Examples 2, 6, 7-9 and 14-17. Applicants note that the humanized MN-14 antibody binds to the same epitope of CEA as the murine MN-14 antibody.

Applicants submit that no new matter is added by amendment.

Claim Rejections – 35 U.S.C. 112 1st Paragraph

Claims 1, 6, 7, 10, 11, 108 and 109 were rejected under 35 U.S.C. 112, 1st paragraph. The Action asserts that the application is, "lacking enablement for any combination therapy (any anti-CEA antibody with any apoptotic agent) producing a synergistic effect in treating human medullary thyroid carcinoma or human colorectal carcinoma." The Action cites the Office Action of 10/22/07 as stating that, "Claim 1 encompasses any anti-CEA Mab (other then MN-14 of Claims 6 and 7), any apoptosis agent (other than those in Claims 10, 11 and 108) and any combination, which are not enabled by the specification..." The Action notes that the Application describes antibodies targeting different epitopes than huMN-14 and asserts that, "Applicants have only disclosed the MN-14 antibody having the instant claimed properties."

Applicants note that claims 6, 7, 109 and 111-114 are limited in scope to the MN-14 antibody, or to antibodies binding to the same epitope as MN-14, and assert that at a minimum, those claims are clearly enabled, as the Action acknowledges that the MN-14 antibody exhibits the instant claimed properties. The Action states that, "the specification, while being enabling for compositions comprising the MN-14 Mab or chimeric or humanized form of the antibody combined with a therapeutic, apoptotic agent, where the MN-14 antibody can chemosensitize a CEA-positive GW-39 (human colon cancer) intrapulmonary cancer in a GW-39 intrapulmonary micrometastasis model..." Thus, there appears to be no basis for the rejection of at least independent claims 109 and 111-114 stated in the Action.

The Action states that, "From the list of apoptotic agents referred to in the specification on p. 6 of the Response, none are shown to produce the effect of d) above [combined effect of antibody and apoptosis agent is more effective than either moiety alone or the sum of either moiety given individually in treating human medullary thyroid carcinoma or human colorectal cancer] when combined with any one of the list of anti-CEA antibodies in treating human medullary thyroid carcinoma or human colorectal cancer."

This is incorrect. The MN-14 antibody is explicitly recited in claims 6, 7, 109 and 111-113 and is clearly within the scope of the claimed combination. Example 2 states that in treating human medullary thyroid tumor cells, "Surprisingly, the effects of MN-14 alone and DTIC alone were not additive...given the results of treatment with 250 μg hMN-14 and 100 μg DTIC alone, one would not predict that the combination of 250 μg hMN-14 and 100 μg DTIC would have such a pronounced effect." Further, "The 75 μg dose of DTIC in combination with this schedule of hMN-14 antibody was significantly more effective than either treatment alone." In conclusion, "Combined therapy of the naked anti-CEA antibody with DTIC augments the anti-tumor effects of antibody or chemotherapy alone, without increased toxicity." Example 7 reiterates that for treatment of medullary thyroid carcinoma, "The 75 μg dose of DTIC in combination with this schedule of hMN-14 was significantly more effective than either treatment alone ($P<0.02$)...combined therapy of the naked anti-CEA MAb with DTIC augments the anti-tumor effects of antibody or chemotherapy alone, without increased toxicity." Example 8 states that, "When combined with DTIC, a surprisingly enhanced level of inhibition of tumor growth occurred relative to either treatment alone."

The Action asserts that, "The specification does not disclose chemosensitizing a human medullary thyroid carcinoma using any anti-CEA antibody much less the MN-14 Mab." Applicants respectfully traverse the assertion. As noted above, Example 2 discloses combination therapy with human medullary thyroid tumor cells and shows a synergistic effect. Examples 7 and 8 show combined therapy with a human MTC (medullary thyroid cancer) xenograft model system and synergistic effects. Paragraph [0243] states that, "TT, a human medullary thyroid cell line, was purchased from the American Type Culture Collection." Paragraph [0246] states that the human tumor cell lines were injected into nude mice to provide a xenograft model system for human cancer therapy. Examples 2, 7 and 8 were performed with the TT human medullary thyroid cancer implanted into nude mice.

Example 9 describes use with colon cancer cells and concludes, "The results show that co-administration of hMN-14 and CPT-11 to nude mice bearing GW-39 lung micrometastases increases survival beyond the effect of either modality alone." Example 14 discloses that for an advanced colon cancer model, "No effect of hMN-14 by itself is apparent under these conditions, and only a modest effect of CPT-11 ($p<0.05$) was observed...Combination therapy with hMN-14 CEA MAb and CPT-11 significantly prolongs survival of an animal with advanced human colonic tumor metastasis." Examples 15-17 confirm the synergistic effects of hMN-14 and CPT-11.

Thus, at least two of the apoptotic agents recited in claims 10 and 11, DTIC and CPT-11, are demonstrated to exhibit the effect of d) when used in combination with the anti-CEA hMN-14 antibody. Applicants note that those agents are two of the seven apoptotic agents listed in claims 10 and 112 and one of the four listed in claim 11. Applicants respectfully assert that this is a sufficient representative number of species to support the genus.

Further, new claim 113 is limited to the combination of a naked humanized MN-14 antibody and an apoptosis agent selected from DTIC and CPT-11. As summarized above, there is clear support in the Specification and working Examples for that combination with the recited characteristics.

The Action states that, "Applicants allege that any combination from any list [of anti-CEA antibodies and apoptotic agents] would have all of the same properties as the limited working examples for anti-CEA antibodies, the MN-14 antibody, that they define in their specification." Applicants do not make such an allegation. Rather, Applicants submit that the evidence summarized above clearly shows that some combinations of anti-CEA antibody and apoptotic agent exhibit the recited properties, and that it would be a matter of routine experimentation for the skilled artisan to determine whether or not any additional combination of anti-CEA antibody and apoptotic agent exhibits the recited properties, using standard assays described in the working Examples of the specification. Further, the scope of claim 113 is limited to those embodiments that are explicitly acknowledged by the Action as enabled by the instant disclosure.

Under MPEP 2164.01, "The standard for determining whether the specification meets the enablement requirement was cast in the Supreme Court decision of *Mineral Separation v. Hyde,* 242 U.S. 261, 270 (1916) which postured the question: is the experimentation needed to practice the invention undue or unreasonable? That standard is still the one to be applied. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)." "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." (citations omitted)

Under MPEP 2164.01, the level of predictability in the art is merely one of eight factors to be considered in determining whether or not undue experimentation is required. The breadth of the claims was discussed in the previous response to office action (which section is incorporated herein by reference) and is limited to a sub-category of anti-CEA antibodies that are unreactive with human granulocytes and have an IgG1 human constant region, in combination with apoptotic agents which are a sub-class of the well-known cancer therapeutic agents. The scope of new claims 111-114 is even further limited. The nature of the invention falls within the field of anti-cancer therapy, a field that has been extensively studied over the past fifty years. The state of the prior art with respect to knowledge of cancer therapeutic agents and anti-cancer antibodies is high. The level of one of ordinary skill, which Applicants assert would include Ph.D. and/or M.D. scientists with expertise in cancer therapy, is also high. The amount of direction provided and the existence of working examples are extensive, as summarized above with respect to the working Examples of the specification. As further demonstrated by those working examples, the quantity of experimentation required to further test any given combination of anti-CEA antibody and apoptosis agent, while perhaps tedious, is not unusual for the field of cancer therapy and is in fact routine in that field. "'The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine...'" [MPEP 2164.06]

Thus, the level of predictability in cancer therapeutics is only one of the factors to consider in determining whether the level of experimentation is undue, and Applicants respectfully submit that the other seven factors weigh heavily in favor of the enablement of the claimed subject matter. Applicants assert that, in analogy with *In re Wands*, "all of the methods needed to practice the invention were well known" and described in detail in the working Examples.

Claim Rejections – 35 U.S.C. 112 2nd Paragraph

Claims 1, 6, 7, 10, 11, 108 and 109 were rejected under 35 U.S.C. 112, 2nd paragraph as indefinite. The Action noted that reference to the administration of naked anti-CEA MAb sensitizing the cancer to the "subsequent" administration of the therapeutic agent is inconsistent with the claim language to a composition comprising both antibody and therapeutic agent, "which apparently requires that both the anti-CEA antibody and at least one therapeutic agent are administered simultaneously by virtue of comprising the composition per se."

Applicants thank the Examiner for pointing out this discrepancy. The claims were amended in the Amendment and Response filed on July 21, 2008, to comply with a requirement of form under 37 C.F.R. 1.116, by deleting recitation of "subsequent" from the claims.

Conclusion

For the reasons stated above, Applicants submit that the amended claims are in condition for allowance and request withdrawal of the rejections.

Respectfully submitted,

/Richard A. Nakashima/
Richard A. Nakashima
Reg. No. 42,023
Phone: 303-828-4924

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